



Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: A prospective cohort study

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Summary

Background: Pulmonary rehabilitation improves outcomes in patients with interstitial lung disease (ILD), however it is unclear whether these effects are long lasting and which patients benefit most.

Methods: Patients with ILD were recruited into this prospective cohort study from three pulmonary rehabilitation programs. Patients completed functional assessments (6-minute walk distance (6MWD), and 4-meter walk time) and surveys (quality of life, dyspnea, depression, and physical activity) before rehabilitation, after rehabilitation, and at six months. Changes from baseline were compared using a paired *t*-test. Independent predictors of change in 6MWD and quality of life were determined using multivariate analysis.

Results: Fifty-four patients were recruited (22 with idiopathic pulmonary fibrosis), 50 patients (93%) completed the rehabilitation program, and 39 returned for six-month follow-up. 6MWD improved 57.6 m immediately after rehabilitation (95% confidence interval (CI) 40.2–75.1 m, $p < 0.0005$), and remained 49.8 m above baseline at six months (95%CI 15.0–84.6 m, $p = 0.005$). The majority of patients achieved the minimum clinically important

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difference for quality of life (51%), dyspnea (65%), and depression score (52%) immediately after rehabilitation, and improvements were still significant at 6-month follow-up for quality of life, depression, and physical activity. A low baseline 6MWD was the only independent predictor of improvement in 6MWD during rehabilitation ($r = -0.49$, $p < 0.0005$). Change in 6MWD was an independent predictor of change in quality of life ($r = -0.36$, $p = 0.01$).

Conclusions: Pulmonary rehabilitation improved multiple short- and long-term outcomes in patients with ILD. While all patients appear to benefit, ILD patients with a low baseline 6MWD had greater benefit from rehabilitation.

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Introduction

Pulmonary rehabilitation is a structured exercise and education program that was developed for patients with chronic lung diseases such as chronic obstructive pulmonary disease (COPD) [1]. Pulmonary rehabilitation is an established treatment for COPD that improves functional capacity (i.e. 6-minute walk distance; 6MWD) and symptoms of dyspnea [2]. More recent research has investigated the role of pulmonary rehabilitation in other chronic lung diseases – in particular interstitial lung disease (ILD) [3–8].

ILD is a group of conditions that cause scarring or inflammation in the lungs, often resulting in significant morbidity and high mortality. Almost all ILDs are characterized by dyspnea and functional limitation, and there are few effective and/or well-tolerated pharmacotherapies for many ILD subtypes. Two small randomized trials and several cohort studies suggest that pulmonary rehabilitation improves functional capacity, quality of life, and dyspnea in ILD [3–8]. However it is unknown whether pulmonary rehabilitation improves other outcomes such as depression, physical activity, and muscle strength, whether these benefits are sustained following rehabilitation, and which patients experience the greatest benefits. Based on these results, recent clinical practice guidelines recommend pulmonary rehabilitation be considered in the management of ILD patients, but note that the quality of the data supporting its use is low and that the long-term benefit remains unclear [9].

We conducted a prospective cohort study of patients with ILD undergoing pulmonary rehabilitation with three main objectives: 1) To determine the short-term and long-term impact of pulmonary rehabilitation on functional and symptomatic outcomes; 2) to define the baseline factors that predict functional change post-rehabilitation; and 3) to characterize the relationship of changes in quality of life to changes in function and symptom scores.

Materials and methods

Study patients

Patients were prospectively recruited between 2010 and 2012 from three pulmonary rehabilitation programs: John Muir Health (Concord, CA, USA), St. Paul's Hospital (Vancouver, BC, Canada), and Seton Medical Center (Daly City,

CA, USA). Patients required a diagnosis of ILD from their treating physician and referral to a participating pulmonary rehabilitation program. ILD diagnosis was recorded using standard criteria where available [9–14]. All patients were required to speak and read English, and be able to return for a six-month follow-up visit. All ILD subtypes were eligible for inclusion. The Institutional Review Boards approved the protocol at each institution (see [Online data supplement](#) for details). All study patients provided written informed consent.

Pulmonary rehabilitation program

All patients were enrolled in a pulmonary rehabilitation program that conformed to standard ATS/ERS recommendations [1]. Programs lasted between six and nine weeks and included twice-weekly sessions of monitored, supervised exercise. The recommended exercise regimen was individually tailored to each patient according to his or her level of functional impairment, severity of ILD (e.g. hypoxemia), presence of comorbid disease, and any other potential factors that could limit intensity or safety of exercise. An exercise prescription was developed for each patient based on medical history, clinical findings and six-minute walk test. The prescription included upper and low extremity training with a designated mode (walking, bicycle and or sitting elliptical trainer), frequency (3–5 times a week), duration of exercise (usually > 20 min but may begin with very short intervals based on clinical findings), and exercise intensity (Borg dyspnea score of 3–6 points) [1]. Patients also attended educational sessions on topics including symptom control, use of oxygen, and disease self-management strategies.

Measurements

Patients were assessed on the first and last scheduled days of pulmonary rehabilitation, and six months following their first pulmonary rehabilitation session. Baseline variables collected at the first visit included age, gender, history of smoking, ILD subtype, the use of medications for treatment of ILD, and the presence of comorbid disease that could impact exercise ability. Patients were specifically asked if they were using azathioprine, bosentan, cyclophosphamide, methotrexate, mycophenolate, acetylcysteine, or prednisone, or if they had a history of cardiac, peripheral vascular, lung airway, pulmonary vascular, neuromuscular,

or arthritic disease. Pulmonary function tests were performed according to standard techniques [15,16].

A functional assessment was performed and symptom-based questionnaires were administered at each study visit. The 6-minute walk distance (6MWD) was performed according to recommended criteria [17], and the percent-predicted 6MWD was calculated based on gender, age, height, and weight as previously reported [18]. The 6MWD has a reported minimum clinically important difference (MCID) of 28 m in patients with IPF [19], and was pre-specified as the primary endpoint. Muscle function was measured using the 4-meter walk time and 4-meter walk speed, which are validated geriatric measures of functional status that are based on the time it takes a patient to walk 4 m at their normal pace [20]. These values are primarily influenced by lower extremity muscle strength [21], and have previously been used in patients with ILD [22]. Community-dwelling older adults typically have walk speeds above 0.90 m/s [23]. Patients were allowed the use of oxygen or gait aids (e.g. cane, walker) during these tests. General level of physical activity was measured using the self-reported Rapid Assessment of Physical Activity questionnaire (RAPA), a 7-point questionnaire that identifies the extent of physical activity conducted on a weekly basis [24].

Symptomatic endpoints included unmodified questionnaires for quality of life, dyspnea, and depression. Quality of life was determined using the St. George's Respiratory Questionnaire (SGRQ) [25,26], a 50-item questionnaire commonly used in ILD clinical research. The performance of the SGRQ has been evaluated in patients with IPF, with an MCID of 5–8 points [27]. Dyspnea was measured using the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) [28]. The UCSD SOBQ is a 24-item questionnaire that has longitudinal construct validity in IPF [29], with a reported MCID of 5 points in patients with chronic respiratory disease [30,31]. Depression was measured by the 15-item Geriatric Depression Scale (GDS) that has an MCID of 1 point [32]. Patients also reported a global assessment of overall change in both their exercise capacity (ability to walk) and quality of life since the beginning of their pulmonary rehabilitation program. This was based on a standardized question with a 15-level response that ranged from "A very great deal worse" to "A very great deal better."

Statistical analysis

Data are described using mean (standard deviation) unless otherwise indicated. Baseline characteristics of patients lost to follow-up were compared to those who completed the study using a Chi-square, *t*-test, or Wilcoxon rank sum test. Comparison of baseline and follow-up measurements was made with repeated measures linear regression, using an unstructured correlation matrix and the "robust" option that provides valid confidence intervals even when specifying an incorrect correlation structure. Repeated-measures analysis is less prone to bias from non-random losses to follow-up compared to complete-case analysis or imputation, and has been used previously in similar analyses [7]. We performed separate analyses for evaluation of

short-term and long-term impact of pulmonary rehabilitation. Short-term impact was analyzed by comparing values obtained at visit 1 (pre-rehabilitation) and visit 2 (post-rehabilitation), and long-term impact by comparing visit 1 (pre-rehabilitation) and visit 3 (follow-up).

Baseline predictors of change in 6MWD were first evaluated on bivariate analysis using a *t*-test or Spearman rank correlation coefficient. Predictors with a bivariate $p < 0.20$ were evaluated in a stepwise multivariate model using backward selection to identify independent predictors of change in 6MWD. A *p* value threshold of 0.20 was used to rule out confounding with greater certainty. A *p* value < 0.05 was required for retention in the final multivariate model. Absolute changes in outcomes over time were calculated by subtracting the visit 1 (pre-rehabilitation) value from the visit 2 (post-rehabilitation). Potential association of change variables with change in SGRQ was tested using bivariate and multivariate analyses as described above. All data analysis was performed using STATA 11.2 (StataCorp, Texas, USA).

Results

Study patients

A total of 54 patients were recruited from the three participating centers (Table 1). The most common diagnosis was IPF ($n = 22$, 41%). Most patients were on medication for their ILD ($n = 31$, 57%), with prednisone used most commonly ($n = 22$, 41%). Patients on average had moderate functional and physiological impairment reflected by the baseline 6MWD, FVC, and DLCO. Ten patients (19%) had a 4-meter walk speed < 0.90 m/s (the lower estimate of walk speed for community-dwelling older adults) [23].

Fifty patients (93%) completed the pulmonary rehabilitation program and 39 patients (72%) returned for the six-month follow-up visit (Fig. 1). Patients attended an average of 15 rehabilitation sessions (range 10–24) over an average of 7 weeks (range 6–9). Four patients died during the study; 2 deaths during the pulmonary rehabilitation period and 2 deaths during the follow-up period. Baseline characteristics of the 15 patients lost to six-month follow-up were similar to those that completed the study (Supplemental Table 1).

Short-term impact of pulmonary rehabilitation

There was short-term improvement following rehabilitation in all functional measures (6MWD, 4-meter walk time, physical activity) and symptom questionnaires (quality of life, dyspnea, depression) (Figs. 2 and 3). 6MWD improved 57.6 m (95% confidence interval (CI) 40.2 to 75.1, $p < 0.0005$), and 34 patients (68%) improved by more than 28 m (the MCID in ILD) [19]. Quality of life score (SGRQ) improved 6.1 points (95%CI 3.7 to 8.6, $p < 0.0005$), with 51% of patients achieving a 5-point or greater improvement, and 38% improving by at least 8 points. The majority of patients achieved the MCID for dyspnea (65%) and depression (52%), and 81% also reported global improvement in their exercise capacity and quality of life (Supplemental Figs. 1(A) and

Table 1 Baseline characteristics.

Variable	Mean (SD) or Number (%) (n = 54)
Age, years	69.4 (10.8)
Male	26 (48%)
Diagnosis	
IPF	22 (41%)
Unclassifiable ILD	8 (15%)
Fibrotic NSIP	5 (9%)
Other ^a	19 (35%)
ILD diagnosed by surgical lung biopsy	20 (37%)
Smoking history	
Current	0
Previous	31 (57%)
Never	23 (43%)
Oxygen therapy	
Continuous	11 (20%)
Exertion only	8 (15%)
Total	19 (35%)
Treatment ^b , %	
Prednisone	22 (41%)
NAC	8 (15%)
Other immune suppressant	7 (13%)
No ILD treatment	23 (43%)
6MWD, m	366 (120)
6MWD, % predicted	77 (23)
4-meter walk time, seconds	3.45 (1.07)
4-meter walk speed, meters/second	1.28 (0.43)
FVC, % predicted	69.2 (21.2)
DLCO, % predicted	46.8 (12.6)

Abbreviations: 6MWD, 6-minute walk distance; DLCO, diffusing capacity of carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NAC, N-acetylcysteine; NSIP, nonspecific interstitial pneumonia; SD, standard deviation.

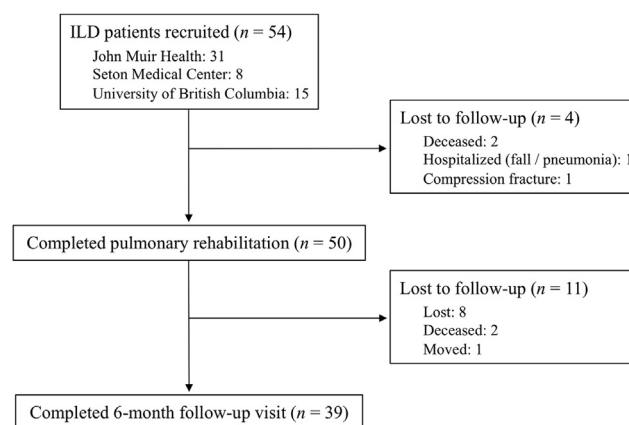
^a Other ILD diagnoses included scleroderma (*n* = 3), sarcoid (3), aspiration-induced ILD (2), hypersensitivity pneumonitis (2), undifferentiated connective-tissue disease-related ILD (2), asbestosis (1), chronic eosinophilic pneumonia (1), dermatomyositis (1), familial pulmonary fibrosis (1), lymphangioleiomyomatosis (1), organizing pneumonia (1), and radiation pneumonitis (1).

^b Other treatments included azathioprine (*n* = 4), mycophenolate (2), cyclophosphamide (1), and methotrexate (1).

2(A)). Effects were similar in the IPF and non-IPF subgroups and across all sites.

Long-term impact of pulmonary rehabilitation

There was long-term improvement in 6MWD, physical activity, quality of life, and depression (Figs. 2 and 3). Average 6MWD remained improved over baseline by 49.8 m (95%CI 15.0–84.7 m, *p* = 0.005) at 6-month follow-up. There was no impact of ILD subtype (IPF vs non-IPF ILD) on the long-term change in 6MWD (*p* = 0.44). Twenty-one patients (55%) maintained an improvement of at least 28 m. The 4-meter walk time decreased non-significantly by

**Figure 1** Study population.

0.24 s (95%CI −0.01–0.49 s, *p* = 0.06). Self-reported physical activity level improved by 0.83 points, as assessed by the RAPA questionnaire (95%CI 0.28 to 1.38, *p* = 0.003). There remained statistically significant improvements over baseline in quality of life (3.6 points, 95%CI 0.2 to 7.0, *p* = 0.04) and depression (1.02 points, 95%CI 0 to 2.1, *p* = 0.05) at 6-month follow-up, however the improvement in dyspnea (4.0 points, 95%CI −1.5 to 9.5, *p* = 0.15) was not statistically significant. There was minimal change in self-reported global assessment of overall change in functional capacity or quality of life compared to pre-rehabilitation (Supplemental Figs. 1(B) and 2(B)).

Predictors of improvement following pulmonary rehabilitation

Baseline 6MWD was the only predictor of change in 6MWD on both bivariate and multivariate analysis (Table 2, Fig. 4). Results were unchanged when using the percent-predicted 6MWD instead of the absolute value. For every 10-meter greater 6MWD pre-rehabilitation, the change in 6MWD post-rehabilitation declined by 2.63 m (95%CI 1.31 to 3.95, *p* < 0.0005), however there was no specific threshold of baseline 6MWD at which rehabilitation could be considered ineffective. Baseline 4-meter walk time and level of physical activity were the only predictors of their subsequent change (Supplemental Fig. 3). The use of prednisone and recent initiation of treatment did not predict change in any outcome variable.

Improvement in quality of life (SGRQ) was associated with an improvement in 6MWD and depression score (GDS) on bivariate analysis (Table 3). Change in 6MWD was the only variable that predicted change in quality of life on multivariate analysis (*R*² = 0.14; Table 3, Supplemental Fig. 4). This association was independent of the initiation of new treatments during the rehabilitation program and was not influenced by ILD subtype.

Discussion

Our data suggest that pulmonary rehabilitation improves functional capacity and quality of life in patients with a variety of ILDs, and that these benefits last for at least 6

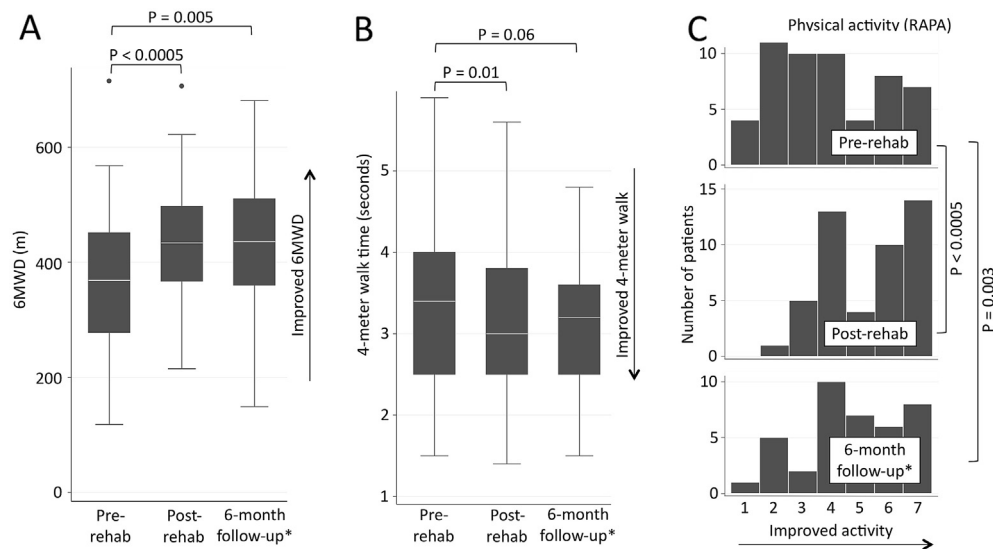


Figure 2 Impact of pulmonary rehabilitation on functional endpoints. Box plots for (A) 6MWD, and (B) 4-meter walk time, and histogram for (C) physical activity level, comparing values pre-pulmonary rehabilitation with post-pulmonary rehabilitation and at 6-month follow-up. *6-month follow-up data refer to measurements recorded six months after initiation of pulmonary rehabilitation. Abbreviations: 6MWD, 6-minute walk distance; RAPA, Rapid assessment of physical activity.

months in most patients. The consistency and magnitude of benefit across endpoints is substantial and markedly better than pharmacological interventions that have been studied in these diseases [33]. These data, combined with previous studies [3–8], suggest that pulmonary rehabilitation should be a first line therapy for patients with ILD.

Previous studies conflict on whether pulmonary rehabilitation is more beneficial in ILD patients with more severe functional impairment [34,35]. This discordance may

be due to differences in inclusion criteria and patient population (e.g. types of ILD, ILD severity, presence of comorbid disease) or study design (cohort vs randomized trial). In our study, patients with worse baseline functional capacity had greater improvements following pulmonary rehabilitation, and we found that patients with baseline walk distances as low as 120 m experienced clinically significant improvement. This suggests that motivated patients with relatively severe functional impairment should

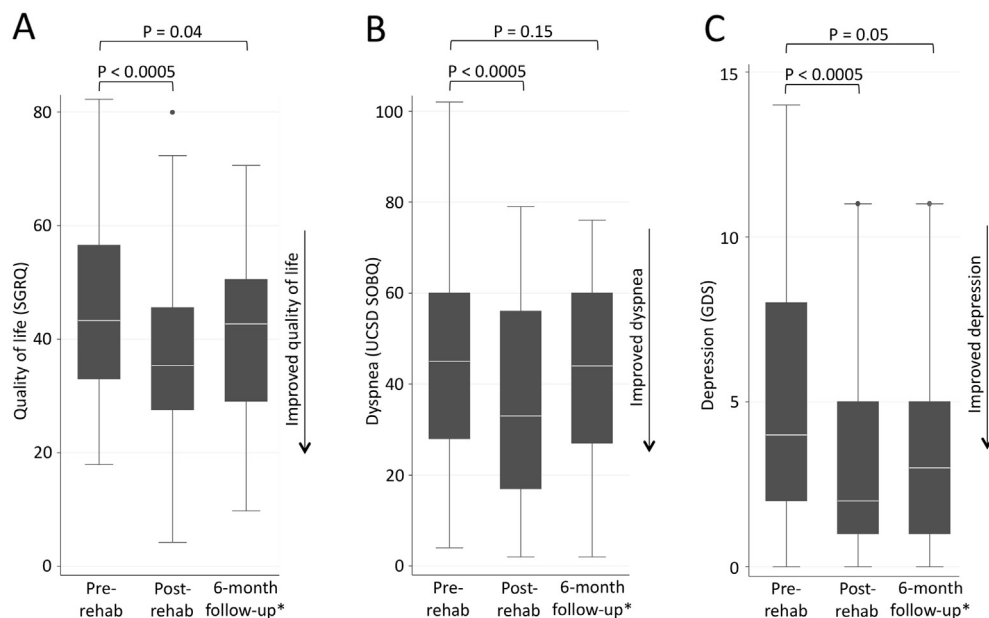


Figure 3 Impact of pulmonary rehabilitation on quality of life, dyspnea, and depression. Box plots for (A) quality of life, (B) dyspnea, and (C) depression, comparing values pre-pulmonary rehabilitation to post-pulmonary rehabilitation and 6-month follow-up. *6-month follow-up data refer to measurements recorded six months after initiation of pulmonary rehabilitation. Abbreviations: SGRQ, St. George's Respiratory Questionnaire; UCSD SOBQ, University of California San Diego Shortness of Breath Questionnaire; GDS, Geriatric depression scale.

Table 2 Baseline bivariate and multivariate predictors of change in 6MWD following pulmonary rehabilitation.

Bivariate predictors	<i>r</i>	<i>p</i> Value
Age, years	0.00	1.00
Male	—	0.07
Diagnosis of IPF	—	0.44
Comorbidity	—	0.96
Recent ILD treatment ^a	—	0.71
Chronic oxygen use	—	0.61
Number of PR sessions attended	−0.24	0.10
6MWD, m	−0.49	<0.0005
6MWD SpO ₂ nadir, %	0.19	0.20
Physical activity (RAPA)	0.24	0.10
4-meter walk time, seconds	−0.16	0.28
FVC, % predicted	0.04	0.81
DLCO, % predicted	0.10	0.54
Echocardiogram RVSP, mmHg	0.17	0.45
Multivariate analysis	Regression coefficient	<i>p</i> Value
6MWD, m ^b	−2.63	<0.0005

r values are reported based on Spearman correlation coefficients between change in 6MWD (follow-up 6MWD – baseline 6MWD) and candidate predictor variables.

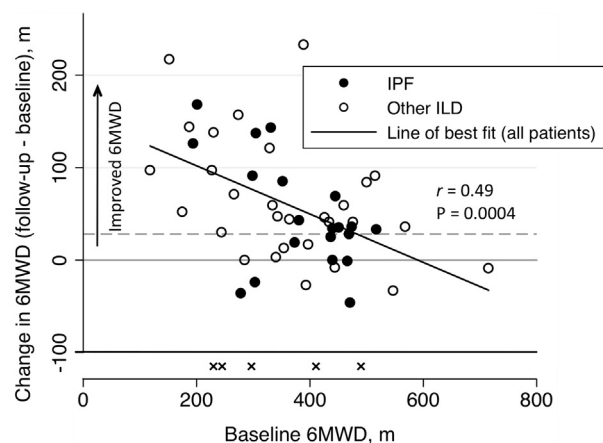
Abbreviations: 6MWD, 6-minute walk distance; DLCO, diffusing capacity of carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PR, pulmonary rehabilitation; RAPA, Rapid Assessment of Physical Activity questionnaire; RVSP, right ventricular systolic pressure.

^a Patients were considered to have recently started ILD treatment if they had started any of prednisone, azathioprine, methotrexate, cyclophosphamide, or mycophenolate within the previous 3 months.

^b Regression coefficient is reported per 10 m of baseline 6MWD (i.e. for each 10 m increase in baseline 6MWD, 6MWD post-rehabilitation declined by 2.63 m).

still be offered pulmonary rehabilitation if the clinical assessment suggests the potential for improvement in functional and/or symptomatic outcomes. Conversely, patients with severe ILD and significant exertional hypoxemia may not be able to train at a high enough intensity to gain similar benefits from rehabilitation. Patients with a high baseline walk distance had less improvement in 6MWD, likely due to either their limited capacity for further improvement (i.e. a ceiling effect) or regression to the mean. However, a high baseline walk distance did not predict lack of improvement in other functional and symptomatic endpoints, suggesting that rehabilitation can still be a valuable intervention in patients with a high baseline functional capacity. Our sample size did not permit detailed subgroup analyses, and there are still limited data on whether all ILD subtypes derive similar benefit from pulmonary rehabilitation.

Most functional and symptomatic improvements were maintained on long-term follow-up, however our results are limited by long-term losses to follow-up of just over a quarter of patients. Most previous studies have handled this limitation by using a complete-case analysis (i.e. removing lost patients from the analysis) or using imputation methods (e.g. last observation carried forward). We believe a repeated measures regression is more appropriate in this

**Figure 4** Association between baseline 6MWD and change in 6MWD after rehabilitation. Association between baseline and change in 6MWD, stratified by ILD subtype (IPF vs non-IPF ILD). The dashed line corresponds to the reported minimum clinically important difference of the 6MWD in IPF. The baseline 6MWD is indicated by an "x" for those patients who did not complete the rehabilitation program. Abbreviations: 6MWD, 6-minute walk distance; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

situation as it mitigates some sources of potential bias that could exist due to preferential dropout of patients that may have benefitted less from rehabilitation. ILD is a progressive disease in many cases, so attenuation of improvements over baseline may represent progression of disease rather than waning effects of rehabilitation. A controlled study is required to fully address this issue. Nonetheless, this attenuation raises the question of whether there are strategies that could promote longer-lasting improvements

Table 3 Bivariate and multivariate correlates of improved quality of life following pulmonary rehabilitation.

Bivariate predictors ^a	<i>r</i>	<i>p</i> Value
6MWD	−0.36	0.01
Physical activity (RAPA)	−0.16	0.28
4-meter walk time, seconds	0.26	0.08
Dyspnea (UCSD SOBQ)	0.20	0.18
Depression (GDS)	0.32	0.03
Multivariate analysis	Regression coefficient	<i>p</i> Value
Change in 6MWD ^b	−0.51	0.01

r values are reported based on Spearman correlation coefficients between change in quality of life (follow-up SGRQ – baseline SGRQ) and candidate predictor variables.

Abbreviations: 6MWD, 6-minute walk distance; GDS, Geriatric Depression Score; RAPA, Rapid Assessment of Physical Activity; SGRQ, St. George's Respiratory Questionnaire; UCSD SOBQ, University of California San Diego Shortness of Breath Questionnaire.

^a All predictors are change in that variable comparing visit 2 (post-rehabilitation) to visit 1 (pre-rehabilitation).

^b Regression coefficient is reported per 10 m of change in 6MWD post-rehabilitation (i.e. for each 10 m increase in 6MWD, the SGRQ declined by 0.49 points).

(e.g. longer duration of rehabilitation, long-term telephone follow-up).

Previous studies have shown that dyspnea severity is a major determinant of quality of life in patients with ILD [36]. However, we found that change in 6MWD (not change in dyspnea) was the strongest correlate of change in quality of life in ILD patients undergoing pulmonary rehabilitation. This is likely due to the fact that rehabilitation improves function (6MWD) more dramatically and durably than dyspnea, and that changes in quality of life are therefore more likely due to these larger changes in function. Although it is not possible to attribute cause and effect to the association between change in 6MWD and change in quality of life, this finding suggests that improving function has an important role in increasing quality of life in patients with ILD. Published data linking change in 6MWD to survival time suggest that improving function may also impact mortality in ILD [37]. Future study is required to address this more completely.

In summary, there is now mounting evidence to support pulmonary rehabilitation as a first line therapy in patients with ILD. Importantly, most patients have clinically meaningful benefit and these effects persist long-term in most patients. Pulmonary rehabilitation is likely complementary to pharmacological therapies, as it works through improvements in fitness and education. This has significant implications for clinicians (who could prescribe pulmonary rehabilitation in addition to any pharmacological therapy) and for clinical trialists (where differences in rates of pulmonary rehabilitation between arms could easily confound efficacy results). Further research is required to confirm which patients benefit most from rehabilitation, determine whether there are components of rehabilitation that are particularly valuable in patients with ILD, define the parameters of endurance and resistance exercise prescription that result in maximal physiological benefits, and explore whether there are strategies that can be used to enhance rehabilitation's long-term benefit.

Source of funding

None.

Conflicts of interest

There are no conflicts of interest for any of the authors.

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CJR takes responsibility for the content of the manuscript, including the data and analysis. The study was conceived by CJR, HRC, and CG. Statistical analysis was performed by CJR. The manuscript was drafted by CJR, HRC, and CG. All authors participated in study design and patient recruitment. All authors reviewed and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2013.11.016>.

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